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EDITORIAL COMMENT

Chronic Total Coronary Occlusion Percutaneous Intervention

The Case for Randomized Trials*

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Chronic total coronary occlusions (CTO) are encountered frequently, found in up to 50% of patients with coronary artery disease (CAD) referred for elective angiography. Treatment strategy for an individual patient is often changed on the basis of the presence or absence of a CTO (1). Percutaneous coronary intervention (PCI) of CTO remains challenging, with observed success rates that are significantly lower than those for non-occluded lesions (2,3). Therefore, it is not surprising that in randomized trials from the BARI (Bypass Angioplasty Revascularization Investigation) trial to the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) study, CTO has endured as the strongest predictor for referral to coronary artery bypass surgery (CABG) rather than randomization.

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Despite the challenges of long procedure times, intensive resource usage, increased radiation and contrast exposure, and reduced success rates, PCI for CTO remains a viable, evolving field with continuing advancements in technique, wires, and catheters and a growing body of published outcomes reports. Current data suggest that successful PCI for CTO is associated with improvement in patient symptoms, quality of life, left ventricular function, and survival, compared with those with unsuccessful CTO PCI (2–11). Whether long-term survival is improved after attempted CTO PCI remains controversial, because no randomized trial of CTO PCI versus medical therapy or CABG has ever been performed. However, indirect data abound and deserve discussion.

An analysis of more than 15,000 patients from the New York State PCI registry demonstrated that incomplete revascularization (IR) was related to lower rates of survival when compared with complete revascularization (12). Chronic total coronary occlusion was frequently encountered in the IR cohort and conferred a greater hazard for death when compared with IR due to subtotal stenoses. Additionally, van der Schaaf et al. (13) demonstrated that the presence of a noninfarct-related artery CTO at the time of primary PCI for ST-segment elevation myocardial infarction is an independent predictor of future mortality. In addition to this indirect evidence, 7 observational studies have demonstrated significant reductions in mortality with successful PCI for CTO, compared with unsuccessful attempts (Table 1) (2,3,5–8,10). In addition, a recent meta-analysis of 13 observational trials also demonstrated a significant reduction in long-term mortality associated with successful CTO PCI, compared with failed attempts (14)

A major limitation of these studies is their observational design, with limited information with regard to potential baseline differences between the successful versus unsuccessful cohorts. The lack of a true randomized, medically treated control group brings up the persistent question of whether the survival benefit demonstrated with successful PCI is, in fact, related to the beneficial effects of opening a chronically occluded vessel versus potential harm conferred to those with failed CTO PCI. Furthermore, it has been hypothesized that failure of CTO PCI is simply a marker for increasing baseline patient and lesion complexity, and therefore the poorer outcomes seen in this group are related to the baseline burden of disease rather than any beneficial effect of CTO recanalization.

In this issue of *JACC: Cardiovascular Interventions*, Mehran et al. (15) report the results of a multicenter observational study examining long-term clinical outcomes of 1,791 patients after PCI for CTO. This was a large well-executed study conducted between 1998 and 2007 with expert CTO operators at highly regarded institutions. An overall procedural success rate of 68% was reported, with success as high as 81% at 1 site. After multivariate adjustment, successful CTO PCI was an independent predictor of reduced cardiac mortality with a strong trend toward lower all-cause mortality. These survival data reinforce the findings of multiple previous observational studies and emphasize that current aggressive PCI attempts and re-attempts with stiff wires and multiple long drug-eluting stents provide excellent long-term results. Safety and efficacy endpoints with drug-eluting stents for CTOs in this trial demonstrated low rates of stent thrombosis and significantly reduced target vessel revascularization, compared with bare-metal stents.

With the existing mature body of observational, "real-world" registry data and a meta-analysis suggesting that successful CTO might prolong life, randomized data are now necessary to further clarify this important issue. A

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Table 1. Observational Studies Demonstrating Significant Reductions in Mortality With Successful PCI for CTO

First Author (Ref. #)	n	Time Period	Follow-Up	Procedural Success Rate	Survival With Successful vs. Failed CTO PCI, p Value
Prasad et al. (3)	1,262	1979–2005	Cumulative 10-yr	67%	72% vs. 77%, p = 0.025*
Suero et al. (2)	2,007	1980–1999	Cumulative 10-yr	69.9%	73.5% vs. 65%, p = 0.001
Noguchi et al. (10)	226	1986–1996	Cumulative 12-yr	59.2%	95% vs. 84%, p < 0.05
Hoye et al. (8)	874	1992–2002	Cumulative 5-yr	65.1%	93.5% vs. 88%, p = 0.02
Olivari et al. (5)	369	1999–2000	1-yr	73.3%	99.7% vs. 96.4%, p = 0.037
Aziz et al. (7)	543	2000–2004	Cumulative 2-yr	69.4%†	98.0% vs. 94.2%, p = 0.049
Valenti et al. (6)	486	2003–2006	Cumulative 4-yr	71%	91.6% vs. 87.4%, p = 0.025

*Approximated from Kaplan-Meier survival curves. After multivariate adjustment, technical failure was not an independent predictor of reduced long-term survival. †Technical success rate.
CTO = chronic total coronary occlusion; PCI = percutaneous coronary intervention.

positive randomized trial comparing optimal medical therapy (OMT) with OMT plus CTO PCI using contemporary techniques would complement existing data and raise the level of evidence favoring aggressive treatment of CTOs with PCI. Ideally, this trial would include patients with a CTO of the proximal or mid left anterior descending coronary artery or CTO of a large dominant right or circumflex artery with a moderate-to-large ischemic burden who have an acceptable amount of angina on medications to minimize crossovers. After baseline data collection and consent, patients would be randomized and followed for >5 years to tabulate survival and cardiovascular outcomes.

Undoubtedly such a trial will be difficult to conduct for multiple reasons. Randomization to a therapy with average success rates in the 75% range will pose a challenge for intention-to-treat analysis. By selecting sites with expert CTO operators performing >75 CTO PCIs/year, this issue could potentially be minimized. Conversely, selection bias directing patients with anatomically favorable CTOs with large ischemic burdens directly to PCI rather than randomization will also have to be monitored and minimized.

The fact that the addition of PCI to OMT for stable CAD has not previously been shown to improve survival in randomized trials is an important consideration. However, CTO has been excluded from these previous trials, and there is evidence from the COURAGE (Clinical Outcomes Utilizing revascularization and Aggressive Drug Evaluation) trial of incremental benefit with PCI with increasing ischemic burden in stable CAD patients (16). Substudies assessing ischemic burden, left ventricular function, and quality of life should be planned, in addition to the evaluation of the effect of CTO PCI on cardiac and total mortality, myocardial infarction, stroke, target vessel revascularization, and CABG. We feel strongly that a randomized trial of this nature would contribute significantly to our understanding of the importance of CTO and refine our treatment approach for CTO patients. Unfortunately, a single randomized trial with 80% power to show a 25% improvement in the expected approximately 8% 5-year mortality with OMT would require randomization of >5,000 patients. If patient-level data were available and entry criteria were consistent, survival data could potentially be pooled from multiple smaller randomized trials separately underpowered for survival analysis.

Currently, the DECISION-CTO (Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients with Chronic Total Occlusion) trial—a randomized trial of PCI versus medical therapy for CTO with a noninferiority, composite end-point design and planned enrollment of 1,100 patients—is being conducted in Asia and will provide us with the first randomized data on CTO PCI. More data from randomized trials are clearly needed to establish the proper positioning of CTO PCI in our treatment strategy.

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REFERENCES

1. Christofferson RD, Lehmann KG, Martin GV, Every N, Caldwell JH, Kapadia SR. Effect of chronic total coronary occlusion on treatment strategy. Am J Cardiol 2005;95:1088–91.
2. Suero JA, Marso SP, Jones PG, et al. Procedural outcomes and long-term survival among patients undergoing percutaneous coronary intervention of a chronic total occlusion in native coronary arteries: 20-year experience. J Am Coll Cardiol 2001;38:409–14.
3. Prasad A, Rihal CS, Lennon RJ, Wiste HJ, Singh M, Holmes DR Jr. Trends in outcomes after percutaneous coronary intervention for chronic total occlusions: 25-year experience from the Mayo Clinic. J Am Coll Cardiol 2007;49:1611–8.
4. Chung CM, Nakamura S, Tanaka K, et al. Effect of recanalization of chronic total occlusions on global and regional left ventricular function in patients with or without previous myocardial infarction. Catheter Cardiovasc Interv 2003;60:368–74.
5. Olivari Z, Rubartelli P, Piscione F, et al. Immediate results and one-year clinical outcome after percutaneous coronary interventions in chronic total occlusions: data from a multicenter, prospective, observational study (TOAST-GISE). J Am Coll Cardiol 2003;41:1672–8.
6. Valenti R, Migliorini A, Signorini U, et al. Impact of complete revascularization with percutaneous coronary intervention on survival in patients with at least one chronic total occlusion. Eur Heart J 2008;29:2336–42.
7. Aziz S, Stables RH, Grayson AD, Perry RA, Ramsdale DR. Percutaneous coronary intervention for chronic total occlusions: improved

survival for patients with successful revascularization compared to a failed procedure. Catheter Cardiovasc Interv 2007;70:15–20.
8. Hoye A, van Domburg RT, Sonnenschein K, Serruys PW. Percutaneous coronary intervention for chronic total occlusions: the Thoraxcenter experience 1992–2002. Eur Heart J 2005;26:2630–6.
9. Cheng AS, Selvanayagam JB, Jerosch-Herold M, et al. Percutaneous treatment of chronic total coronary occlusions improves regional hyperemic myocardial blood flow and contractility: insights from quantitative cardiovascular magnetic resonance imaging. J Am Coll Cardiol Intv 2008;1:44–53.
10. Noguchi T, Miyazaki MS, Morii I, Daikoku S, Goto Y, Nonogi H. Percutaneous transluminal coronary angioplasty of chronic total occlusions. Determinants of primary success and long-term clinical outcome. Catheter Cardiovasc Interv 2000;49:258–64.
11. Grantham JA, Jones PG, Cannon L, Spertus JA. Quantifying the early health status benefits of successful chronic total occlusion recanalization: results from the FlowCardia's Approach to Chronic Total Occlusion Recanalization (FACTOR) trial. Circ Cardiovasc Qual Outcomes 2010;3:284–90.
12. Hannan EL, Racz M, Holmes DR, et al. Impact of completeness of percutaneous coronary intervention revascularization on long-term outcomes in the stent era. Circulation 2006;113:2406–12.
13. van der Schaaf RJ, Vis MM, Sjauw KD, et al. Impact of multivessel coronary disease on long-term mortality in patients with ST-elevation myocardial infarction is due to the presence of a chronic total occlusion. Am J Cardiol 2006;98:1165–9.
14. Joyal D, Afilalo J, Rinfret S. Effectiveness of recanalization of chronic total occlusions: systematic review and meta-analysis. Am Heart J 2011;160:179–87.
15. Mehran R, Claessen BE, Godino C, et al. Long-term outcome of percutaneous coronary intervention for chronic total occlusions. J Am Coll Cardiol Intv 2011;4:952–61.
16. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation 2008;117:1283–91.

Key Words: chronic total coronary occlusions ■ percutaneous coronary intervention ■ randomized trial.